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(21) Application No. 1810/76 (22) Filed 16 Jan. 1976
(31) Convention Application No. 541 906
(32) Filed 17 Jan. 1975 in
(33) United States of America (US)

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SPECIFICATION NO 1476717

The following amendments were allowed under Section 29 on 17 April 1979

Page 2, line 28, page 8, line 15, *delete* at least 0.001% *insert* from 0.001% to 0.025%

Page 2, line 61, page 3, line 3, *delete* 0.500 *insert* 0.025

Page 3, line 21, *delete* generally

Page 3, line 22, *delete* 0.5% *insert* 0.025%

Page 3, *delete* lines 25 to 27, *insert* 0.01 to 0.025% by weight. Besides being effective and safe on

Page 3, line 88, page 8, line 72, *delete* 0.05% *insert* 0.025%

Page 4, *delete* lines 7 to 18 and 39 to 84

Page 4, *for* Examples 4, 5, 6 and 13 *read* 2, 3, 4 and 5

Page 5, *for* Examples 14 to 19 and 21 *read* 6 to 12

Page 5, *delete* whole of Column 8 heading 20 and Columns 9 to 12 headings 22 to 25

Page 6, lines 25, 29 and 41 *after* formulations *insert* having various tretinoin strengths

Page 6, Table 1, both Columns headed Gel *delete* 64 and 80

Page 6, Table 1, page 7, Tables II and III both Columns headed Gel *delete* —**

Page 7, Table II both columns headed Gel *delete* 62 and 78

Page 7, Table III both columns headed Gel *delete* 62

Page 7, end of Table III *delete* **No test was run

Page 8, *delete* lines 24 to 29

Page 8, *for* claims 4 to 17 *read* 2 to 15

Page 8, line 30 for 3 read 1

Page 8, lines 33 and 34 *delete* any one of the preceding claims *insert* claim 1 or claim 2

Page 8, lines 38, 42 and 45 *for* 5 *read* 3

Page 8, lines 43 and 46 *for* 6 *read* 4

Page 8, line 53, *for* 9 *read* 7

Page 8, line 91, *for* 16 *read* 14

THE PATENT OFFICE
15 May 1979

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(19)

(54) TRETINOIN IN A GEL VEHICLE FOR ACNE TREATMENT

(71) We, JOHNSON & JOHNSON, a Corporation organised and existing under the laws of the State of New Jersey, United States of America, of 501 George Street, New Brunswick, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a gel formulation of tretinoin (trans-retinoic acid, or vitamin A acid). More particularly, it relates to gel formulations of tretinoin which are effective when tretinoin is present in low concentrations. The product is particularly suitable for the treatment of dermatological disorders such as acne vulgaris.

Acne vulgaris is a dermatological disorder prevalent in adolescence. It appears most commonly on the face and trunk of the patient. The basic lesion of acne is the comedo or "backhead" of a pilosebaceous follicle. In its mildest form, only few comedones are present, but in its severe form, a multiplicity of severe, persistent comedones are present. Permanent scarring is frequently a consequence of the severe form of acne.

Acne occurs when there is a filling up of the follicle with a rather tough keratinous material. It is this impaction of horny material which forms the whitehead and blackhead. As a result of bacterial growth in these horny impactions, the follicle ruptures, initiating the inflammatory phase of the disease in which pustules, papules, cysts and nodules are formed.

A variety of methods have been used for the treatment of acne, including the use of peeling agents, hormone therapy for female patients antibacterial therapy and general surgical skin planing.

Although systemic administrations of hormones and antibacterials have been used with some success, until recently none of the topical treatments have been particularly effective.

Vitamin A acid (tretinoin) has been applied topically, (Beer, Von P., "Untersuchungen über die Wirkung der Vitamin A-Säure", *Dermatologica, 124:* 192—195, March, 1962 and Stüttgen, G., "Zur Lakalbehandlung von Keratosen mit Vitamin A-Säure", *Dermatologica, 124:* 65—80, February, 1962) in the treatment of certain hyperkeratotic disorders which are responsive to high oral doses of Vitamin A. Among the disorders treated by Beer and Stüttgen were patients with acne; however, these investigators reported no effective improvement in the acne disorder with Vitamin A acid treatment. British Patent Specification No 906,000 discloses a cosmetic preparation containing Vitamin A acid for the regulation of the cornification processes of human skin, but no mention is made of the use of such preparation for the treatment of acne.

Recently, however, it has been demonstrated that prolonged topical application of Vitamin A acid is effective in the treatment of acne (Kligman, A. M., "Topical Vitamin A acid in Acne Vulgaris", *Arch Derm., 99:* 469—476 April 1969). In such treatment a composition was used in which Vitamin A acid was dispersed in a water-miscible (substantially oil- and fat-free) liquid carrier having high solvating action. The topical application of this Vitamin A acid composition caused irritation of the skin in the treated areas (see United States Patent Specification No 3,729,568).

More recently, it has been found that acne can be effectively treated with a cream formulation containing tretinoin, or Vitamin A acid. A cream formulation is generally more acceptable to patients than a liquid formulation from the point of view of aesthetics and ease of application. Moreover, another important advantage of the cream form of tretinoin is that it reduces the side effects normally associated with the topical application of tretinoin. These side effects, erythema, stinging and itching, may be sufficient to cause the patient to discontinue the application of tretinoin before it can be fully effective upon the acne.

Notwithstanding these advantages, cream formulations containing tretinoin posses some undesirable attributes. One of these undesirable attributes is the difficulty in uniformly applying sufficient amounts of the active ingredient to the lesion of acne to be effective and, at the same time, to avoid local excesses, surface spread or pooling into facial creases, the nasolabial folds and corners of the mouth where the cream may cause erythema, stinging and itching. Another undesirable attribute of cream formulations of tretinoin is their relative instability, often necessitating the use of refrigeration or antimicrobial preservatives to prevent microbiological contamination, as well as special additives to maintain physical stability.

We have now discovered a vehicle for tretinoin from which tretinoin is readily available for absorption by the skin, and an acne treatment composition which is effective at low concentrations of tretinoin, which thereby avoids the side effects associated with the use of acne treatment formulations having high concentrations of tretinoin.

According to the present invention there is provided a gel formulation for topical application comprising at least 0.001% by weight of tretinoin, and a vehicle system consisting essentially of an organic solvent which is ethanol, isopropanol, propylene glycol, or a mixture thereof, an effective amount of a pharmaceutically acceptable antioxidant soluble in the organic solvent and an effective amount of a pharmaceutically acceptable gelling agent solvated in the organic solvent.

The ethanol used as the solvent may be absolute or 95% by volume ethyl alcohol. The antioxidant is preferably a butylated hydroxytoluene (BHT), a butylated hydroxyanisole (BHA), ascorbic acid (Vitamin C), propyl gallate, or α-tocopherol (Vitamin E). The gelling agent is preferably (1) an acidic carboxy polymer, such as those available under the trade names Carbopol 934 and Carbopol 940, neutralized with an organic amine, such as β-alanine or diisopropanol amine, (2) hydroxyethylcellulose or (3) hydroxypropyl cellulose. (CARBOPOL is a Registered Trade Mark).

The organic solvent may comprise a mixture of ethanol and propylene glycol, isopropanol and propylene glycol, or ethanol and isopropanol.

A general formula encompassing tretinoin gel formulations within the scope of my invention is set forth below. (Unless otherwise indicated herein, all amounts are in weight percent.)

General Gel Formula in % w/w

Tretinoin	0.001—0.500
Antioxidant(s)	0.010—0.100
Gelling agent(s)	0.5 —5.000
Dye(s) and/or perfume oil(s)	0.0 —0.750
Sunscreen(s)	0.0 —2.500
Topical corticosteroid	0.0 —2.000
Antimicrobial(s)	0.0 —3.000
Organic solvent	q.s. to 100,000

It has been unexpectedly found that tretinoin gel formulations of the present invention are more effective in the treatment of acne conditions than tretinoin cream formulations having a similar tretinoin concentration. It also has been found that cream formulations having low concentrations of tretinoin may have little or no efficacy against acne when compared to the same vehicle with no tretinoin, whereas, gel formulations having the same low concentrations of tretinoin exhibit high efficacy against acne, the efficacy level often being almost the same as exhibited by gels with higher tretinoin concentrations. This is a surprising and unexpected discovery and the reason for it is not fully understood. However, without the intention of being bound by it, the following explanation is provided.

It is known in the healing art that solid drugs intended for absorption by the skin are not absorbed directly but must be dissolved by a vehicle or by skin fluids. It is also well known that drugs in the microfine form are more readily available for absorption. Upon evaporation of the solvent carrier drugs are deposited on the skin in different forms, such as, for example large crystals or a film. Tretinoin is not soluble in common vehicles such as, for example, water. It is soluble in several vehicles if the vehicles are made alkaline. However, in alkaline solutions tretinoin is very unstable. The only vehicles in which tretinoin is both soluble and at the same time stable are the organic solvents. Most of these organic solvents quickly evaporate and leave behind the large crystalline deposit of tretinoin. It is then up to the skin fluids to solvate the crystalline tretinoin for absorption by the skin. The rate of absorption mainly depends on the solubility of tretinoin in skin fluids. Obviously, the larger the crystals, the lower their solubility in skin fluids and the slower their absorption through the skin. It is believed that the tretinoin is deposited on the skin from the gel formulations of the present invention in a microfine form, thus promoting the penetration of tretinoin through the skin by virtue of its relative ease of solubility in skin fluids as compared to that of a larger crystal form. This would enable a lower strength tretinoin gel to deliver subcutaneously an effective quantity of the tretinoin that is equivalent to that delivered by a preparation of higher strength from which the tretinoin is not deposited on the skin in a micro-fine form.

Tretinoin gel formulations in accordance with the present invention have been found to have good chemical and physical stability for at least 18 months at 37° C.

The tretinoin gel formulations of the present invention, in general, comprise from 0.001 weight % to 0.500 weight % of tretinoin; from 0.01 weight % to 0.10 weight % of the antioxidant, from 0.5 to 5.0 weight % of the gelling agent, and from 84 to 99 weight % of the solvent. Optionally, minor amounts of agents such as dyes, perfumes, and sunscreens, which are commonly used in topical pharmaceutical compositions, may be added. Furthermore, topically active medicaments such as the anti-inflammatory corticosteroids and antimicrobials may also be incorporated.

While the tretinoin gel compositions of the present invention have been described herein primarily as suitable for use in treating acne, it will be understood that these compositions are effective generally for treating dermatological conditions where tretinoin is indicated. The concentration of tretinoin in the gel compositions of the present invention is generally within the range of from 0.001 to 0.5% by weight. The preferred range for the concentration of tretinoin in the gel formulation is from 0.005 to 0.05% by weight, from 0.01 to 0.025% by weight being particularly preferred. Besides being effective and safe on application to the skin, concentrations within these preferred ranges offer substantial costs savings.

The antioxidants which may be used in the compositions of the present invention are those which are soluble in ethanol, isopropyl alcohol, propylene glycol or mixtures thereof; are non reactive to the gelling agents, tretinoin, and other components of the formulations; and are safe for human topical use. Preferably from 0.01 to 0.10% by weight, most preferably from 0.025 to 0.075% by weight of antioxidant is used.

The gelling agents employed in the compositions of the present invention are those capable of being solvated or those which can be modified to be capable of being solvated in the solvents utilized in these compositions and which are commonly used in pharmaceutical preparations for topical applications. While there are numerous pharmaceutically acceptable gelling agents for topical use, they are either only marginally acceptable such as, for example, ethyl cellulose or they are not suitable for the purposes of the present invention such as, for example, methylcellulose and the salts and derivatives of alginic acid because they do not form a satisfactory gel. Preferably from 0.5 to 5.0% by weight of a gelling agent, more preferably from 0.5 to 3.0% by weight, is used. The particularly preferred gelling agents are hydroxyethylcellulose, having a viscosity of from 3,500 to 50,000 cps. when a 2 percent aqueous solution is measured at 20° C. using Brookfield Viscometer, Model LVF, with Spindle No. 30 at 30 RPM, available under the trade name Natrosol from Hercules Powder Co. Inc., Wilmington, Delaware; hydroxypropyl cellulose having a molecular weight from 100,000 to 1,000,000, available under the trade name Klucel from Hercules Powder Co. Inc.; an acidic carboxy polymer, such as those available under the trade names Carbopol 934 and Carbopol 940 from B. F. Goodrich Chemical Co., Cleveland, Ohio, neutralized with an organic amine, such as β-alanine and diisopropanol amine. The neutralization of the acidic carboxy polymer with an organic amine enables the acidic carboxy polymer to be solvated by the organic solvent used in the invention. While partial neutralization is sufficient to effect solvation, preferably the amount of organic amine used to neutralize the acidic carboxy polymer will be approximately equivalent by moles to the acidic carboxy polymer present in the formulation, and may even be in excess of the molar equivalent amount.

A particularly preferred composition according to the invention comprises from 0.005 to 0.05% by weight of tretinoin, from 84 to 99% by weight of an organic solvent which is ethanol, isopropanol, propylene glycol or a mixture thereof, from 0.025 to 0.075% by weight of an antioxidant which is a butylated hydroxytoluene, a butylated hydroxyanisole, ascorbic acid, propyl gallate, or α-tocopherol, and from 0.5 to 3.0% of a gelling agent which is hydroxyethylcellulose, hydroxypropyl cellulose or an acidic carboxy polymer which is neutralized with β-alanine or diisopropanol amine.

The compositions of the invention may be prepared by various methods practiced and well known in the art. In general, the desired amount of antioxidant is dissolved in the solvent, followed by the addition and subsequent solvation of the desired amount of tretinoin. The desired amount of gelling agent is added in small quantities under low shear agitation until solvation occurs and the mixture gels. When an acidic carboxy polymer such as Carbopol 934 or Carbopol 940 is used as the gelling agent, the neutralization with an organic amine is accomplished by adding the desired amount of an organic amine after the last portion of the acidic carboxy polymer is added to the mixture and sufficient amount of time allowed for its dispersion. Low shear agitation continues until solvation occurs and the gel is formed.

The procedure preferably should take place at room temperature, i.e. at about 25° C. If desired, additional materials, such as dyes, perfumes, sunscreens, and corticosteroids may be incorporated into the formulations by adding and mixing them with the solvent prior to the addition of the gelling agent.

The following Examples provide further illustration of compositions of the invention, without thereby limiting the scope thereof.

EXAMPLE 1.

	% w/w
Tretinoin	0.001
Butylated hydroxytoluene	0.01
Hydroxypropyl cellulose	2.0
Propylene glycol	q.s. to 100.0

EXAMPLE 2.

	% w/w
Tretinoin	0.5
Butylated Hydroxyanisole	0.10
Hydroxypropyl cellulose	5.00
Propylene glycol	q.s. to 100.0

EXAMPLE 3.

	% w/w
Tretinoin	0.05
α-tocopherol	0.05
Hydroxyethylcellulose	2.5
Ethanol	q.s. to 100.0

EXAMPLE 4.

	% w/w
Tretinoin	0.005
Butylated hydroxytoluene	0.05
Carbopol 940	3.0
β-alanine	3.0
Ethanol	q.s. to 100.0

EXAMPLE 5.

	% w/w
Tretinoin	0.025
Butylated hydroxytoluene	0.05
Hydroxypropyl cellulose	3.0
Ethanol	q.s. to 100.0

EXAMPLE 6.

	% w/w
Tretinoin	0.025
Butylated hydroxytoluene	0.05
Carbopol 940	3.00
Diisopropanol amine	3.00
Isopropanol	q.s. to 100.0

EXAMPLE 7.

	% w/w
Tretinoin	0.1
Butylated Hydroxyanisole	0.05
Hydroxyethylcellulose	4.0
Perfume Oil	0.25
Dye	0.25
Ethanol—Isopropanol 50/50 mixture by weight	q.s. to 100.0

EXAMPLE 8.

	% w/w
Tretinoin	0.15
α-tocopherol	0.05
Hydroxypropyl cellulose	0.5
Hydrocortisone	0.5
Ethanol—Propylene glycol 50/50 mixture by weight	q.s. to 100.0

EXAMPLE 9.

	% w/w
Tretinoin	0.05
Butylated hydroxytoluene	0.05
Hydroxypropyl cellulose	3.00
Propylene glycol/isopropanol 50/50 mixture by weight	q.s. to 100.0

EXAMPLE 10.

	% w/w
Tretinoin	0.05
Butylated hydroxytoluene	0.05
Hydroxypropyl cellulose	3.00
Propylene glycol/ethanol 50/50 mixture by weight	q.s. to 100.0

EXAMPLE 11.

	% w/w
Tretinoin	0.05
Butylated hydroxytoluene	0.05
Hydroxypropyl cellulose	3.00
Ethanol/isopropanol 50/50 mixture by weight	q.s. to 100.0

EXAMPLE 12.

	% w/w
Tretinoin	0.05
Butylated hydroxytoluene	0.05
Carbopol 934	1.5
β-alanine	1.5
Propylene glycol/ethanol 50/50 mixture by weight	q.s. to 100.0

EXAMPLE 13.

	% w/w
Tretinoin	0.02
Butylated Hydroxytoluene	0.05
Carbopol 934	1.5
Diisopropanol amine	1.5
Propylene glycol/isopropanol 50/50 mixture by weight	q.s. to 100.0

TABLE OF ADDITIONAL EXAMPLES

Examples	14	15	16	17	18	19	20	21	22	23	24	25
Tretinoin	0.01	0.01	0.002	0.025	0.025	0.02	0.05	0.025	0.05	0.5	0.5	0.5
BHT			0.05				0.05					
BHA				0.05								
Vitamin C		0.05										
Vitamin E	0.05					0.05		0.05	0.05	0.05		
Propyl gallate					0.05						0.05	0.10
Propylene glycol	97.44						48.40		95.90		25.45	
Ethanol			48.72	97.93	95.93	95.93	50.00			94.40	70.00	34.65
Isopropyl alcohol		97.44	48.72					99.18				60.00
Carbopol 934					2.0							
Carbopol 940						2.0						
Hydroxyethylcellulose	2.0		2.0					0.75		3.5		4.5
Hydroxy propylcellulose		2.0		2.0			0.75		3.0		4.0	
β-alanine					2.0							
Diisopropanol amine						2.0						
Dye		0.25	0.25				0.25					0.25
Perfume	0.25	0.25					0.25					
Hydrocortisone	0.25		0.25				0.25		1.0	2.0		

In use, the tretinoin gel composition of the present invention is generally applied daily until the desired relief is obtained. The number of daily applications depends on the severity of the acne condition that the patient has, and may vary between one and three applications. Normally the treatment requires at least 8—12 weeks. However, acne in its mildest form i.e., only a small number of comedones, may be substantially cleared in four to six weeks. More severe cases may require two to three months or longer.

It has been observed in use that the gel formulations of the present invention were easy to apply, remaining on the areas that were treated with little tendency to run and pool or to produce disturbing irritation at the angles of the mouth or nasolabial folds. Furthermore, and quite unexpectedly, only momentary stinging rather than prolonged discomfort, following application, was generally experienced as compared to previously used dosage forms.

Clinical studies have been conducted by different investigators on the relative effectiveness of the gel formulations of the present invention containing tretinoin in combination with butylated hydroxytoluene, hydroxypropyl cellulose and ethanol in comparison to cream formulations containing tretinoin in combination with stearic acid, isopropyl myristate, polyoxy 40 stearate, stearyl alcohol, xanthan gum, sorbic acid, and butylated hydroxytoluene. The studies were double-blind, parallel clinical studies comparing gels and creams having the same concentrations of tretinion, against each other and against their respective control vehicle or placebo without tretinoin. Tables I to III summarize the combined results of these studies.

Table I compares overall effectiveness data of the identified cream and gel formulations on the treatment of acne whether it be in the form of comedones, pustules, papules, cysts or nodules. Table II compares effectiveness data of creams and gels in reducing comedones. Table III compares effectiveness of creams and gels in reducing papules. It is to be noted that the result should be interpreted in an order-of-magnitude sense and not an absolute sense. The reason for this is the variables affecting the outcome of the result, such as, different investigators, different groups of patients, time, and geographic or climatic factors.

TABLE I

Percent of Patients Having a Good or Excellent Clinical Evaluation

Tretinoin Strength	Number of Patients*		Percent	
	Cream	Gel	Cream	Gel
.000%	121	66	28	39
.010%	59	41	31	83
.025%	65	67	46	83
.050%	125	64	62	80
.100%	63	—**	70	—**

TABLE II

Percent Reduction of Comedones

Tretinoin Strength	Number of Patients*		Percent	
	Cream	Gel	Cream	Gel
.000%	122	60	35	48
.010%	62	38	44	67
.025%	67	65	44	77
.050%	126	62	61	78
.100%	63	—**	54	—**

TABLE III

Percent Reduction of Papules

Tretinoin Strength	Number of Patients*		Percent	
	Cream	Gel	Cream	Gel
.000%	122	60	23	34
.010%	62	38	13	62
.025%	67	65	52	60
.050%	126	62	53	62
.100%	63	—**	64	—**

*Some of the patients in the studies had only comedones and some had only papules, although most patients had both. Therefore, Table I, which summarizes the investigators' evaluation of overall effectiveness, would be expected to show somewhat greater total number of patients than either of Tables II and III, and does so with respect to the "gel" patients. However, one of the investigators, omitted overall evaluation for the "cream" patients, providing only separate evaluation with respect to comedones and pustules. Hence the lower number of total patients in the cream column in Table I as compared to Tables II and III.

**No test was run.

Referring to Tables I, II and III, it is apparent that there is a higher percent improvement in acne conditions when treating patients with a zero strength or placebo gel than with a zero strength or placebo cream. The reason for this difference, no doubt, is in the cleansing or disinfecting nature of the carriers: while both carriers effect reduction of acne conditions due to the cleansing capabilities of some of their components, the gel carrier, having an alcohol, propylene glycol or mixtures of alcohols and propylene glycol therein, exhibit higher antibacterial or cleansing properties.

It is also apparent from Table I, II and III that the gel formulations of various tretinoin concentration effect unexpectedly greater improvement in reducing acne conditions than do the cream formulations of the same tretinoin concentration. In fact, a ten fold increase in tretinoin concentration is necessary in the cream formulations to achieve the effect of the 0.01% gel formulations both in the reduction of comedones and papules and in overall clinical improvement. As explained previously herein, this is thought to be due to the availability of tretinoin in micro-fine forms for absorption through the skin.

The gel formulations of tretinoin described

with reference to the above Examples possess good physical and chemical stability without refrigeration and without special additives or antimicrobial preservatives being incorporated therein.

These gel formulations also have other desirable qualities such as being cosmetically elegant, having a perceptible drying effect or at least making no contributions to the oiliness of acne patients' skin, and allowing accurate application of effective amounts of tretinoin to the acne lesion.

WHAT WE CLAIM IS:—

1. A gel formulation for topical application comprising at least 0.001% by weight of tretinoin, and a vehicle system consisting essentially of an organic solvent which is ethanol, isopropanol, propylene glycol or a mixture thereof, an effective amount of a pharmaceutically acceptable antioxidant soluble in the organic solvent and an effective amount of a pharmaceutically acceptable gelling agent solvated in the organic solvent.

2. A formulation as claimed in claim 1 which contains from 0.001 to 0.5% by weight of tretinoin.

3. A formulation as claimed in claim 2 which contains from 0.005 to 0.05% by weight of tretinoin.

4. A formulation as claimed in claim 3 which contains from 0.01 to 0.025% by weight of tretinoin.

5. A formulation as claimed in any one of the preceding claims wherein the gelling agent is hydroxyethylcellulose, hydroxypropyl cellulose or an acidic carboxy polymer which is neutralized with an organic amine.

6. A formulation as claimed in claim 5 wherein the gelling agent is incorporated therein in an amount of from 0.5 to 5.0% by weight.

7. A formulation as claimed in claim 5 or claim 6 wherein said acidic carboxy polymer is neutralized with β-alanine.

8. A formulation as claimed in claim 5 or claim 6 wherein said acidic carboxy polymer is neutralized with diisopropanol amine.

9. A formulation as claimed in any one of the preceding claims wherein the antioxidant is a butylated hydroxyanisole, a butylated hydroxytoluene, α-tocopherol, ascorbic acid, or propyl gallate.

10. A formulation as claimed in claim 9 wherein the antioxidant is incorporated therein in an amount of from 0.01 to 0.10% by weight.

11. A formulation as claimed in any one of the preceding claims wherein the organic solvent is present in an amount of from 84 to 99% by weight.

12. A formulation as claimed in any one of the preceding claims which additionally comprises at least one additive which is a dye, perfume oil, sunscreen, antimicrobial or topical corticosteroid.

13. A formulation as claimed in any one of the preceding claims wherein the organic solvent is a mixture of ethanol and propylene glycol, isopropanol and propylene glycol, or ethanol and isopropanol.

14. A gel formulation for topical treatment of acne vulgaris consisting essentially of from 0.005 to 0.05% by weight of tretinoin, from 84 to 99% by weight of an organic solvent which is ethanol, isopropanol, propylene glycol or a mixture thereof, from 0.025 to 0.075% by weight of an antioxidant which is a butylated hydroxytoluene, a butylated hydroxyanisole, ascorbic acid, propyl gallate, or α-tocopherol, and from 0.5 to 3.0% of a gelling agent which is hydroxyethylcellulose, hydroxypropyl cellulose or an acidic carboxy polymer which is neutralized with β-alanine or diisopropanol amine.

15. A formulation as claimed in claim 1 substantially as hereinbefore described with reference to any one of the Examples.

16. A process for the preparation of a gel formulation as claimed in claim 1 substantially as hereinbefore described.

17. A gel formulation whenever prepared by a process as claimed in claim 16.

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